



Year: 2017

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Abstract: BACKGROUND/AIMS: Gender-specific differences between patients on renal replacement therapy have so far rarely been investigated. In the present study we aimed to describe gender-specific differences in a large cohort of peritoneal dialysis (PD) patients. METHODS: Clinical information for all patients who started PD at our center has been collected since the start of the PD-program in 1979. We used Cox regression to examine associations between technique failure and gender. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs). RESULTS: A total of 745 patients (315 women and 430 men with a median age of 57 years; IQR 43-67) started PD between 1979 and 2015 in our center. Women were significantly younger at PD start 54 (40-65) years vs. 58 (47-68) years, $p < 0.001$. Within the last almost 15 years, more men than women started PD, but technical survival rates were significantly better in female compared to men (HR=0.662, CI 95% (0.496-0.885) $P=0.005$). Cardiovascular events were the main cause of death over the study period in both sexes, but decreased over time. Additionally, death due to PD-associated peritonitis decreased significantly over the three decades in both sexes. CONCLUSIONS: Our data suggest that technical survival rates were significantly better in female compared to men over three decades and death due to cardiovascular events and PD-associated peritonitis decreased significantly over the three decades in both sexes.

DOI: <https://doi.org/10.1159/000477449>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-142789>

Journal Article

Published Version



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Originally published at:

Kitterer, Daniel; Segerer, Stephan; Braun, Niko; Alscher, M Dominik; Latus, Joerg (2017). Gender-specific differences in peritoneal dialysis. *Kidney Blood Pressure Research*, 42(2):276-283.

DOI: <https://doi.org/10.1159/000477449>

Original Paper

Gender-Specific Differences in Peritoneal Dialysis

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Key Words

Peritoneal dialysis • Gender • Gender difference • Technical failure • Death

Abstract

Background/Aims: Gender-specific differences between patients on renal replacement therapy have so far rarely been investigated. In the present study we aimed to describe gender-specific differences in a large cohort of peritoneal dialysis (PD) patients. **Methods:** Clinical information for all patients who started PD at our center has been collected since the start of the PD-program in 1979. We used Cox regression to examine associations between technique failure and gender. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** A total of 745 patients (315 women and 430 men with a median age of 57 years; IQR 43–67) started PD between 1979 and 2015 in our center. Women were significantly younger at PD start 54 (40–65) years vs. 58 (47–68) years, $p < 0.001$. Within the last almost 15 years, more men than women started PD, but technical survival rates were significantly better in female compared to men (HR=0.662, CI 95% (0.496–0.885) $P=0.005$). Cardiovascular events were the main cause of death over the study period in both sexes, but decreased over time. Additionally, death due to PD-associated peritonitis decreased significantly over the three decades in both sexes. **Conclusions:** Our data suggest that technical survival rates were significantly better in female compared to men over three decades and death due to cardiovascular events and PD-associated peritonitis decreased significantly over the three decades in both sexes.

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Introduction

Peritoneal dialysis (PD) was introduced successful in the early 1980s as an additional routine modality for renal replacement therapy (RRT) in end-stage renal disease (ESRD) [1].

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From 1997 to 2008 the number of PD patients increased in developing countries more than in developed countries, and in 2008, 11% of the global dialysis population was performing PD [2-4]. Several studies showed an initial survival benefit of PD in the first 2 years compared to hemodialysis [2, 5, 6], and very recent data from the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) showed that patient survival has improved over the last 20 years for both PD and hemodialysis (HD) [7]. However, between 1997 and 2008 in developed countries the proportion of patients on PD decreased [2]. Little data exists about gender-specific differences in the characteristics, treatment and outcomes for individuals on RRT. In a recent analysis of over 200 000 HD patients in 12 different countries, the International Dialysis Outcomes and Practice Patterns Study (DOPPS) showed a global trend towards fewer women than men treated with HD for RRT of end-stage renal disease [8]. Carrero et al. found no gender-specific differences in the cardiovascular outcomes of hemodialysis patients at the beginning of RRT [9] and registry data from Spain suggests that women on PD had a higher risk for mortality from infection than did men [10]. We aimed to investigate gender-specific differences in a large cohort of PD patients from the early years of PD until 2015.

Materials and Methods

Study population

All patients undergoing surgery for PD catheter insertion at the Robert-Bosch-Hospital, Stuttgart, Germany, from January 1979 to December 2015 were analyzed retrospectively. Clinical information regarding any underlying disease, gender, date of birth, time of starting PD, type of PD (system, type of solution), and catheter implantation at hospital was collected prospectively from the start of the PD program in 1979. After catheter implantation, initiation and training at hospital provided by a PD nurse, a proportion of patients were treated as outpatients at ambulatory nephrologist. A total of 745 incident patients were identified and included in the current study. Clinical data were available for 620 patients at the time when PD was terminated (e.g. death, technique failure, recovery of renal function, or kidney transplantation) or end of the study period (December 2015). Patients still on PD (115 patients) were of course not included in the analysis for death (study design is shown in Fig. 1).

The Ethical Commission of the Medical University of Tuebingen approved this study (Ethical Approval/Registration Number #020/2016B02). The analysis was performed retrospective without written or verbal informed consent to participate in this study. Due to the long study period and the retrospective anonymous analysis of the data, nevertheless the lack of informed consent has been approved by the local ethics committee.

Termination of PD and technical failure

Termination of PD: Patients were followed until they switched to hemodialysis (HD), received a kidney transplant, recovered of renal function, died during PD, were lost to follow-up or until the end of study period (December 2015). Technique failure was defined as any transfer from PD to HD that lasted for ≥ 30 days [11] and was censored for death and kidney transplantation. After an interruption of ≥ 30 days, the subsequent period of PD was excluded from further analysis.

Statistical analyses

The statistical analyses were conducted with SPSS, version 24.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 6.0 (GraphPad, San Diego, CA, USA) software. All continuous variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as means (with standard deviation, SD) and skewed variables were presented as medians (with interquartile ranges (IQR)). Comparisons between the three groups were performed with Fisher's exact test (two-tailed). Cox proportional hazard model was used for analyzing technical failure. Analysis was adjusted for age. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs). P values (two-tailed) <0.05 were considered significant. In the technique survival analysis, patients who recovered renal function, died, received a kidney transplant, or were still on PD were censored from the analysis.

Results

Between 1979 and 2015 a total of 745 patients, 315 women and 430 men, with a median age of 57 years (IQR 43–67), started PD. Diabetic nephropathy (21%) and glomerulonephritis (15%) were the most common underlying diseases for ERDS. Regarding baseline characteristics, no differences were present between male and female patients, except the younger age of women at start of PD (54 (40–65) years vs. 58 (47–68) years, $p < 0.001$), higher number of male patients with ESRD due to hypertensive nephrosclerosis and IgA nephropathy and more women than men in the group of patients with interstitial nephritis, NSAID and amyloidosis as underlying diseases for ERDS. Patient characteristics and the causes of ESRD are shown in detail in Table 1. Within the first 20 years, gender ratio was approximately equal whereas in the later years more men than female started PD (Fig. 2).

Table 1. Patient characteristics and causes of end-stage renal disease (ESRD)

Patients	Men	Women	p
	58% (430)	42% (315)	
Age at PD initiation	58 (47–68)	54 (40–65)	<0.001
Cause of ESRD (when available)*	N=412	N=303	
Diabetic nephropathy	120 (29)	74 (24)	0.174
HT nephrosclerosis	55 (13)	21 (7)	<0.01
ADPKD	22 (5)	28 (9)	0.053
IgA nephropathy	45 (11)	16 (5)	<0.01
Other glomerulonephritis	49 (12)	41 (14)	0.569
Hereditary nephropathy	11 (3)	8 (3)	1.000
Multisystem disease ^a	9 (2)	14 (5)	0.086
Amyloidosis	4 (1)	10 (3)	<0.05
TMA	4 (1)	6 (2)	0.337
Others ^b	74 (18)	58 (19)	0.697
NSAID induced	1 (0)	7 (2)	<0.05
Obstructive/reflux NP	9 (2)	9 (3)	0.631
Interstitial nephritis	3 (1)	10 (3)	<0.05
Cardio-renal Syndrome	6 (1)	1 (0)	0.248

*Data was not available in 12 female and 18 male patients. ^a Including systemic lupus erythematosus and ANCA-associated vasculitis. ^b Including atrophic kidneys or unknown. HT, hypertensive; PD, peritoneal dialysis; KTX, kidney transplantation; HD, hemodialysis; NP, nephropathy, ADPKD, autosomal dominant polycystic kidney disease, TMA, thrombotic microangiopathy, NSAID, non-steroidal anti-inflammatory drug, PD, peritoneal dialysis, values in brackets represent percentages

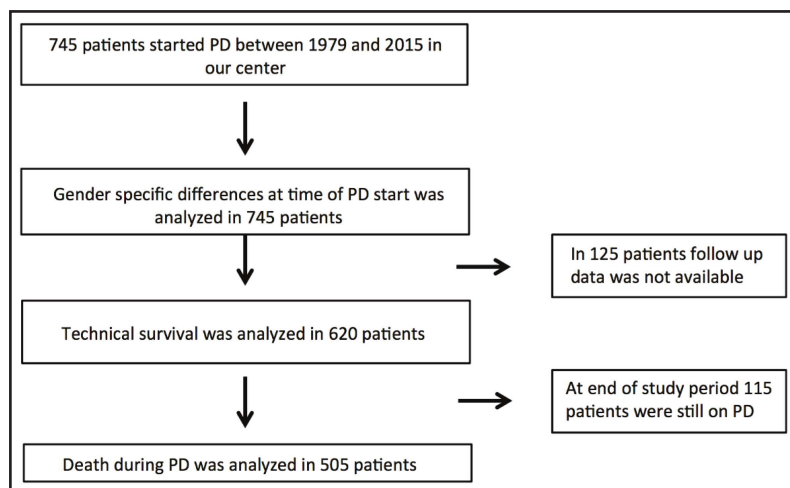


Fig. 1. Study design.

Over the whole study period 187 out of 505 PD patients (37%) died. Cardiovascular events were the main cause of death in both sexes (Table 2) and decreased over time from 28% in the first decade to 6% in the second decade and 8% in the last decade ($p < 0.0001$, respectively). In total, more men compared to women died on PD during the study period (45% vs. 29%, $p < 0.0001$). Death due to PD-associated peritonitis was in total more common in men compared to women ($p < 0.05$, Table 2) and decreased as well over time from 9% in the first decade to 3% in the second decade and 2% in the last decade ($p < 0.05$ and $p < 0.01$, respectively).

Technical survival curve of female compared to male using the Cox proportional hazard model adjusted by age showed statistical significant lower technical failure rates in female compared to men (HR=0.662, CI 95% (0.496-0.885) $P=0.005$ (Fig. 3).

Table 2. Causes of death on PD. Values in brackets are percentages

	Men	Women	p
Total	226/505 (45)	148/505 (29)	$p<0.0001$
Cardiovascular	82/505 (16)	56/505 (11)	$p<0.05$
PD-associated peritonitis	30/505 (6)	16/505 (3)	$p<0.05$
Other infection	24/505 (5)	16/505 (3)	n.s.
Primary disease	14/505 (3)	24/505 (5)	n.s.
Malignancy	16/505 (3)	6/505 (1)	$p=0.05$
Others/not known*	60/505 (12)	30/505 (6)	$p<0.01$

*Including end-stage liver disease, gastrointestinal bleeding, death after surgery, trauma

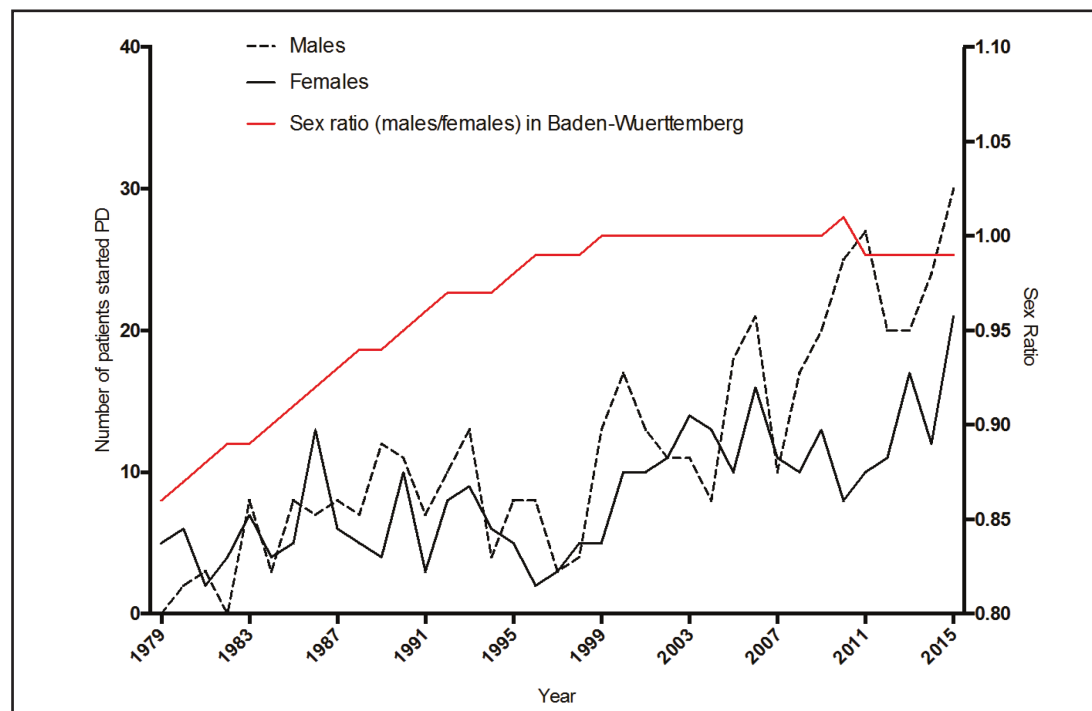


Fig. 2. Number of females and males started PD between 1979 and 2015 in our center. The red line shows the ratio of men compared to women in the federal state Baden-Wuerttemberg during the study period in the 40-70 years aged population. The first 20 years were explained by the consequences of World War II.

Discussion

To the best of our knowledge this is the first study to investigate gender-specific differences in patients on PD and represents the largest historic cohort of PD patients in Germany.

According to the 2011 census, approximately 51% of the German population was women, a proportion that has hardly changed over the last 10–20 years. Up to the age of 50 the proportion of males predominates, but over the age of 50 an increasing surplus of women is seen [12]. Recently, the International Dialysis Outcomes and Practice Patterns Study (DOPPS) showed, that in HD patients worldwide a disproportion between men and women exists. Between 1996 and 2012 the DOPPS investigated more than 200 000 HD patients in 12 different countries and found that fewer women than men were undergoing hemodialysis. This was consistent with national hemodialysis registry data, despite higher proportions of women

in the general population across all age groups in all countries [8].

In our cohort, we found an increasing proportion of men in the last 15 years starting PD. Remarkably, in these last 15 years, the median age was 59 years (46 - 69) and the predominance of men was in direct contrast to the preponderance of women over 50 in the general population. Therefore our retrospective analysis is consistent with the large prospective DOPPS study in HD patients. Therefore, all efforts must be made to re-examine our findings prospectively. Perhaps the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) study may be able to shed light on the subject (it is noteworthy that Germany

is not part of the study) [13]. As men outnumber women in both forms of dialysis this might reflect either disease specific factors (e.g. prevalence of non diabetic renal diseases in men, accumulation of risk factors and progression of chronic kidney disease [14]) as well as differences in the use of dialysis in female patients. One would then have to hypothesize that the incidence has changed since the first decade.

Death on PD decreased over the three decades and not very surprisingly, cardiovascular events were the main cause of death. As expected more men died on PD because of cardiovascular deaths compared to women in the last 15 years. The most likely explanation for this gender-specific difference in deaths on PD is the greater proportion of men on PD in this time period observed in the present study. On the other hand, previous analyses showed a higher risk of death due to infection while on PD in men than in women [10], which we could not find in our study. Some studies analyzed the mortality risk of men versus women on hemodialysis [8, 15-17], whereas few studies have addressed this question in PD patients. An ERA-EDTA registry analysis reported that younger women have a higher risk of dying from non-cardiovascular causes [16]. The main finding of the previous studies in hemodialysis patients was that the mortality advantage of women in the general population is lost in hemodialysis patients. It is obvious that our analysis does not have the power to clarify the risk for death for men and women on PD but the data suggest that at least the last 15 years women had no disadvantages with regard to death.

The main cause for technique failure is PD-associated peritonitis [18-21]. Another important issue is the fact that centers with a large number of PD patients have better outcomes [22-26].

Gender-specific differences in technique failure are controversial. Several studies have shown that gender was not associated with technique failure [27-30], however, one large

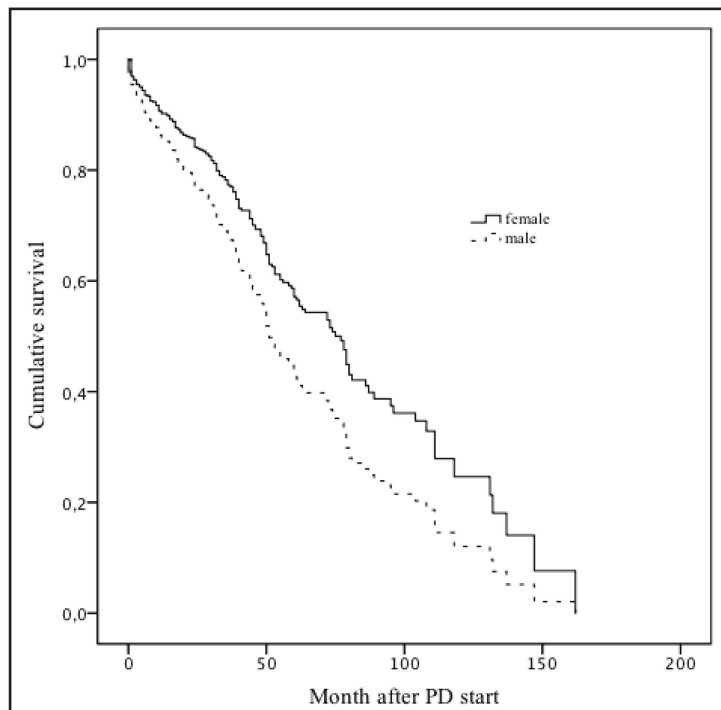


Fig. 3. Cox survival curves for technical survival adjusted for age (censored by death, kidney transplantation, improvement of kidney function and lost of follow up) in female compared to men PD patients starting PD between 1979 and 2015 in our center.

study from the Australia and New Zealand registry and an analysis of a cohort of US patients found a higher risk of technique failure in PD for men than for women [11, 31]. This was consistent with our findings. It was speculated that men might be more dependent on others to maintain their care, leaving them more sensitive to modality failure [11]. Unfortunately, as stated by Shen et al. [11], we have no information on assistance from caregivers. It is noteworthy, that in our study population, women were significantly younger compared to men at start of PD, but it seems unlikely for us that the difference of four years might explain the better technical survival rates solely.

Nevertheless, as shown by Guest et al. up to now there is still a long lasting discussion whether encapsulating peritoneal sclerosis occurs more frequently in female PD patients compared to the men [32]. This outlines the need for studies dealing with gender aspects among PD patients.

Our study has potential limitations, which have to be addressed. First, our data were retrospective and from a single center in Germany (all patients received their PD catheter in this single hospital), with all known limitations and a possible selection bias and a center-specific effect [24]. Of course, the medical and nursing teams have changed over time and that might have affected patients dialysis modality choice. Second, because of the long study period and the German healthcare system, the clinical data e.g. regarding peritonitis rates and follow-up beyond termination of PD are incomplete. Therefore, we cannot investigate a gender-specific difference in outcomes in our cohort of patients; however, our data do suggest some important differences between the genders. There were no differences in regard to age and gender in patients in whom no follow-up was available compared to the group of patients with follow-up data. Third, after catheter implantation, initiation and training at hospital provided by a PD nurse, most of the patients were treated as outpatients at ambulatory nephrologist. Therefore, e.g. reasons for terminating PD might be center specific and must be taken into account by interpreting our results. Fourth, unfortunately, there exist no national wide registry for dialysis patients in Germany, therefore we could not give information about the number of patients reaching ESRD over the study period.

The fundamental question to be answered is whether there is discrimination against women starting dialysis? Or do fewer women need dialysis because of different disease patterns, or do women choose not to start dialysis? These questions could not be answered with this study – likewise PDOPPS would not be able to answer these questions completely.

Conclusion

Our data suggest that technical survival rates were significantly better in female compared to men over three decades and death due to cardiovascular events and PD-associated peritonitis decreased significantly over the three decades in both sexes.

Disclosure Statement

The authors have no commercial associations or sources of support that might pose a conflict of interest.

Acknowledgement

Joerg Latus and Daniel Kitterer are supported by the Robert-Bosch Foundation (Stuttgart, Germany). Stephan Segerer is supported by grants by Fundação Pesquisa e Desenvolvimento Humanitario and the Else Kröner-Fresenius Stiftung.

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